

# Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH)

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**Diagnosis, treatment-monitoring and follow-up of children and adolescents with X-linked hypophosphatemia (XLH)**

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25    **Abstract**

26    Early diagnosis, optimal therapeutic management and regular follow up of children with X-linked hypophosphatemia (XLH) determine their long  
27    term outcomes and future quality of life. Biochemical screening of potentially affected newborns in familial cases and improving physician's  
28    knowledge on clinical signs, symptoms and biochemical characteristics of XLH for *de novo* cases should lead to earlier diagnosis and treatment  
29    initiation. The follow-up of children with XLH includes clinical, biochemical and radiological monitoring of treatment (efficacy and complications)  
30    and screening for XLH-related dental, neurosurgical, rheumatological, cardiovascular, renal and ENT complications. In 2018, the European  
31    Union approved the use of burosumab, a humanized monoclonal anti-FGF23 antibody, as an alternative therapy to conventional therapy (active  
32    vitamin D analogues and phosphate supplements) in growing children with XLH and insufficiently controlled disease.  
33    Diagnostic criteria of XLH and the principles of disease management with conventional treatment or with burosumab are reviewed in this paper.

34

35    **Keywords**

36    X-linked hypophosphatemia (XLH), alfacalcidol, burosumab, osteomalacia, rickets

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38

39

## 1. INTRODUCTION

X-linked hypophosphatemic rickets (XLHR, OMIM 307800), a rare genetic disease due to inactivating mutations in the *PHEX* gene (Phosphate Regulating Gene with Homologies to the Endopeptidase on the X chromosome MIM #300550) is the most common form of hypophosphatemic rickets with an incidence of 1:20000(1,2).

*PHEX* is expressed in osteocytes and odontoblasts and inactivating *PHEX* mutations result in increased synthesis and secretion of fibroblast growth factor 23 (FGF23). Part of the pathophysiological mechanism that underlies XLHR is impaired proximal renal phosphate reabsorption and reduced 1- $\alpha$ -hydroxylation of 25-OH vitamin D due to the excess action of FGF23(3,4).

Children affected by XLH present with rickets, severely impaired mineralization of bone (osteomalacia) and teeth, and other signs and symptoms ultimately caused by excess FGF23, with the typical biochemical profile of hypophosphatemia, renal phosphate wasting and reduced calcitriol [1,25(OH)<sub>2</sub> vitamin D] concentration.

Early diagnosis and optimal management and follow-up of children and adolescents with XLH are the keys to successful outcomes, which determine the future quality of life of these patients. To date, large-scale natural history studies of XLH are lacking, which makes it is difficult to distinguish possibly inevitable long-term complications due to the underlying condition from sequelae of inadequate management. The burden of disease observed in today's adult XLH patients(5,6) suggests that late diagnosis and inadequate management contribute to adverse outcomes.

The aim of this review is to highlight the need for early diagnosis and optimal management so that children with XLH become healthier future adults.

## 64 2. DIAGNOSIS OF XLH

65

66 Disease awareness of physicians and affected family members leads to early diagnosis and thus early treatment initiation. Early diagnosis of  
67 XLH is of major importance since early treatment initiation leads to better outcomes such as improved linear growth and final height, bone mass  
68 accrual, fewer bone deformations and better dental health(7–11).

69 Two diagnostic settings need to be distinguished.

70

### 71 2.1 Diagnosis of familial cases of XLH

72 About 85-90% of familial cases of hypophosphatemic rickets are associated with *PHEX* gene mutations(10,12–19). XLH due to *PHEX*  
73 mutations follows an X-linked dominant inheritance pattern(2). Thus, affected fathers transmit the disease to all of their daughters and none of  
74 their sons. Affected mothers have a 50% risk of having an affected daughter or son. In the setting of familial XLH, potentially affected newborns  
75 should be biochemically screened and treatment should be initiated as soon as the diagnosis is made in order to prevent rachitic changes, leg  
76 bowing and short stature. If appropriately managed, it is unlikely that these patients develop active rickets and consequent orthopedic  
77 complications (figure 1).

78 However, even in familial XLH cases diagnosis can be delayed. Unfortunately, adult patients are often lost to follow-up and may not have been  
79 informed or may have incompletely understood the inheritance pattern. This is illustrated by the median age at diagnosis of XLH in familial  
80 cases of 1.3 years, ranging from 0.1 to 14.3 years (n=58; unpublished data obtained from patients followed at the French reference center of  
81 Bicêtre, Paris, and(20)). During the transition from pediatric to adult care, it is crucial to explain the inheritance pattern to adolescents and  
82 young adults with childbearing potential.

83

84 In babies born to parents affected with XLH, biochemical screening should be performed as soon as possible after the 1<sup>st</sup> week of life or  
85 certainly at first presentation to their family doctor. Screening includes serum phosphate, creatinine and alkaline phosphatase (ALP), and  
86 urinary phosphate and creatinine. Diagnosis of XLH is suspected if the serum phosphate level is below the normal range for newborns and if  
87 renal phosphate wasting is documented using the calculated renal phosphate reabsorption rate(21–23). It is essential that serum phosphate

88 and ALP concentrations are interpreted based on reference ranges for newborns and infants as these are physiologically higher than those for  
89 adults(24,25). Although clinical and radiological signs of rickets (figure 1) are often lacking in those babies, ALP may be found at the upper level  
90 of normal. Once diagnosis is made, the patient needs to be referred to a pediatrician specialized in bone disease (e.g. a pediatric  
91 endocrinologist) and treatment should be initiated immediately. The genetic diagnosis, i.e. *PHEX* sequencing, confirms the diagnosis; it may be  
92 done on cord blood or on a sample drawn after birth. Waiting for genetic results should not delay the start of treatment. Of note, a serum  
93 phosphate level within the normal range during the first months of life does not rule out the diagnosis and, in the absence of genetic diagnosis,  
94 the biochemical screening should be repeated including serum phosphate and ALP.

95

## 96 **2.2 Diagnosis of *de novo* cases of XLH**

97 Children with XLH due to *de novo* *PHEX* mutations, i.e. one third of the patients, are usually diagnosed after a diagnostic odyssey. Mean age at  
98 diagnosis is  $3.9 \pm 3.1$  years, ranging from 0.9 to 13.1 years (unpublished data, Bicêtre, Paris) (figure 2a).

99

### 100 **2.2.1 Revealing symptoms**

101 Diverse clinical presentations may lead to the diagnosis of XLH. The most frequent and typical presentation is rickets (figure 1) which manifests  
102 as long bone deformities, especially leg bowing, delayed walking, waddling gait and bone/joint pain developing progressively once toddlers start  
103 standing and walking. In those patients, pediatricians and/or orthopedic surgeons are often the first specialists that are consulted because of leg  
104 deformities. As a certain degree of leg bowing in toddlers is considered physiological (26) (figure 2b), the first consultation may not always lead  
105 to a diagnostic work-up and therefore diagnosis is delayed until symptoms worsen. Stunted growth may be the revealing symptom in *de novo*  
106 XLH children (14% of cases in Bicêtre center; unpublished data); noteworthy, growth velocity is always poor at the time of diagnosis in those  
107 children. Rarely, the diagnosis of rickets is made from radiographs taken for other reasons, e.g. systematic screening of hip dysplasia in  
108 France.

109

### 110 **2.2.2 Diagnostic criteria**

111 Any leg bowing (*genu varum* or *valgum*) whether or not associated with poor statural growth, and widening of the metaphysis (ankles and  
112 wrists) should lead to a radiological and biochemical work-up. Tooth abscesses or facial cellulitis occurring on apparently healthy teeth suggest  
113 poor dentin mineralization(9). Radiological signs of XLH are detailed in this issue by C. Adamsbaum and colleagues. Briefly, radiographs of the  
114 hand, knees and lower limbs show the long bone deformities, abnormal growth plates with widened and frayed metaphyses. In contrast to other  
115 forms of rickets, bone cortices appear dense(20,27). At the time of diagnosis, fractures are uncommon in children and adolescents.  
116 Biochemical criteria (table 1) for the diagnosis of XLH include:

- 117 – serum phosphate below the normal threshold for age(28,29) associated with renal phosphate wasting, e.g. reduced calculated maximal  
118 tubular reabsorption of phosphate as a function of glomerular filtration rate (TmP/GFR)(21). Of note, the fractional tubular resorption of  
119 phosphate (TRP) value may be within the normal range in children with XLH, and in the presence of hypophosphatemia only the  
120 TmP/GFR is diagnostic;
- 121 – ALP levels above the upper limit of normal for age, indicating rickets/osteomalacia. In children, the measure of total ALP is used, in  
122 contrast to adults, in whom bone ALP should be measured preferably(20,30). Although ALP levels are elevated in XLH children and  
123 adolescents, the increase is not in the order of magnitude as seen in vitamin D deficiency rickets, defects in calcitriol synthesis or  
124 calcitriol receptor mutations (commonly called the vitamin D receptor) (figure 2c);
- 125 – parathyroid hormone (PTH) levels in the normal or upper normal range; any mild increase in PTH may be caused by underlying  
126 additional vitamin D or dietary calcium deficiency;
- 127 – normal serum calcium, and low urinary calcium excretion;
- 128 – exclusion of other proximal or distal tubular wasting disorders;
- 129 – exclusion, and otherwise prior correction, of vitamin D or dietary calcium deficiency.

130 In summary, the key to correct diagnosis of *de novo* XLH cases is good knowledge of the clinical signs and symptoms and the correct use of  
131 age-adjusted biochemical investigations to distinguish various forms of rickets.

132

133 The diagnosis of XLH may be confirmed by the measurement of elevated levels of intact FGF23. However, FGF23 concentrations may be  
134 inappropriately normal and this does not exclude the diagnosis. Patients with XLH produce levels of FGF23 that are well below those of patients  
135 with oncogenic osteomalacia (31,32). FGF23 levels are influenced by several factors including phosphate intake(33,34).  
136

### 137 **2.3 Genetic confirmation of XLH**

138 The final confirmation of XLH is obtained through genetic analysis which identifies mutations in the *PHEX* gene in ~70% of patients with  
139 hypophosphatemic rickets, and 85-90% of patients when the disease is familial (2,12,16,19,35–46). Whenever possible, genetic analysis is  
140 recommended. Different types of *PHEX* mutations exist including point mutations, splice-site mutations, small and large deletions, deletions of  
141 pseudo-exons, and mosaicism, suggesting that several techniques or strategies may be necessary to reach a final diagnosis(18,39,47–51).  
142

### 143 **3. SEVERITY OF DISEASE AND COMPLICATIONS**

144 We now have enough evidence to inform patients that XLH is a multisystemic disorder that may be associated with several complications  
145 including

- 146 – tooth abscesses, taurodontism (enlarged pulp chambers and body of tooth), facial cellulitis and periodontitis(52,53);
- 147 – premature fusion of cranial sutures leading to dolichocephaly and/or craniosynostosis; in some cases, patients may present with  
148 increased intracranial pressure, Chiari 1 malformation, syringomyelia, papillary oedema or neurological signs(54–61) ;
- 149 – hearing impairment(20,62–65);
- 150 – short stature: final height below -2SD is found in ~50% of patients adequately treated by conventional therapy(10,11,20,24,66–74);
- 151 – reduced muscle function due to hypophosphatemia(75,76);
- 152 – joint and bone pain

153  
154 At the time of diagnosis, XLH children should undergo a thorough work-up to assess the severity/extent of the disease(20,30) including:



- 155 – measuring rickets severity, judged by inter-malleolar and intercondylar distances, 6MWT (6-minute walking test) as a global dynamic  
156 measure, serum ALP and PTH levels, serum and urinary calcium and phosphate concentrations, and hand, standing long leg and/or  
157 knee X-rays;
- 158 – assessing possible complications of the disease, i.e. craniosynostosis and its neurological complications(55,60), hearing impairment(62),  
159 abnormal dental mineralization(9), growth retardation(69), and reduced muscle function(76);
- 160 – measuring renal function (glomerular and tubular) and morphology before the start of therapy through kidney ultrasound and detailed  
161 biochemical work-up.

162

#### 163 **4. DIFFERENTIAL DIAGNOSIS**

164

165 Once the diagnosis of rickets is confirmed by clinical, biochemical and radiological criteria, and the diagnosis of nutritional rickets and vitamin D  
166 resistant rickets (VDDR1-3), all of which are associated with secondary phosphate wasting due to high PTH levels, have been ruled out, other  
167 causes of hypophosphatemic rickets should be considered in patients who do not carry a *PHEX* variant, even if they display an elevated FGF23  
168 level. The different causes of hypophosphatemic rickets are described in table 3.

169 Several rickets-like diseases that may lead to progressive bone deformities, abnormal gait and metaphyseal irregularities need to be excluded.  
170 These conditions may be found in the presence of low ALP levels, e.g. hypophosphatasia(77) or normal levels of ALP, e.g. healed nutritional  
171 rickets, Blount's disease or Schmid type metaphyseal dysplasia(78).

172

#### 173 **5. DISEASE MANAGEMENT**

##### 174 **5.1 Principles of disease management**

175 Once the diagnosis of XLH is established, the objective of the treatment is to restore the lower limb biomechanic axis and gait, improve growth,  
176 bone and teeth mineralization and muscular function. Disease management should also include social aspects, patient/family education and  
177 support. In addition, during follow up, the multidisciplinary team will aim at preventing the development of endocrine, orthopedic, rheumatologic,

178 metabolic, cardiovascular and renal complications. So far, international recommendations that could guide physicians in the management of  
179 these rare patients are lacking. However, some reports have been published including extensive physicians' expertise(20,30).

180 The patient pathway will involve different health and social disciplines throughout infancy, childhood and adolescence. We suggest that patients  
181 are seen at regular intervals by multidisciplinary teams lead by a pediatric expert in bone diseases, who will liaise with the patient's local  
182 healthcare providers (general practitioners/ pediatricians), a pediatric radiologist, orthopedic surgeon, physiotherapist, dentist and orthodontist.  
183 Additional professions may be required, e.g. pediatric neurosurgeon, ear, nose and throat (ENT) specialist, ophthalmologist, dietician, social  
184 worker and psychologist.

185

186 Two different therapies are currently available for XLH: active vitamin D analogues combined with phosphate supplements, and burosumab, the  
187 monoclonal fully human anti-FGF23 antibody. These treatments have different therapeutic objectives and outcomes, and therefore require  
188 different management as highlighted in table 2.

189

## 190 **5.2 Conventional treatment with vitamin D analogues and phosphate supplements**

191 For decades, the association of active vitamin D analogues (alfacalcidol or calcitriol) and phosphate supplements using multiple daily dosing  
192 was the only treatment option for children with XLH. The objective of this therapy is to counteract the calcitriol deficiency secondary to FGF23  
193 excess and to compensate renal phosphate wasting. Medication doses reported in the literature, most of which date back over 20 years, vary  
194 widely, from 10-80 ng/kg/day of calcitriol and 30-180 mg/kg/day of elemental phosphate(8,20,67,79–83). Advice on treatment, based on recent  
195 reviews(20,30) and the authors' expertise is shown in table 2.

196

197 This therapy has demonstrated its efficacy to:

- 198 – decrease ALP concentrations to the upper limit of normal in ~ one year(20);
- 199 – improve bone deformity, bone pain and gait in 30 to 60% of patients(11,66,67,80,82,84–86);
- 200 – improve growth velocity in the magnitude of ~ 1 standard deviation(8,10,11,20,66–72,79,84,87);

201 – significantly improve dentin mineralization and therefore decrease teeth abscesses and oral complications in affected  
202 children(7,9,20,88,89).

203 Improvement in some of these outcomes, i.e. linear growth, final height, radiological features of rickets and oral health(7,10,11,90), has been  
204 associated with early treatment initiation and longer duration of treatment.

205 Many limitations to this therapy have been identified over the years and should be known by the caring physician, including:

- 206 – the absence of correction of the phosphate wasting with continued hypophosphatemia(20,30,80,85);
- 207 – the risk of nephrocalcinosis and/or urolithiasis; large doses of active vitamin D and oral phosphate supplements have both been  
208 associated with an increased rate of nephrocalcinosis in children(67,91–95);
- 209 – the risk of hyperparathyroidism; large oral doses of phosphate supplements are associated with the development of secondary and  
210 tertiary hyperparathyroidism by yet unknown mechanisms (8,86,91,92,96–100)
- 211 – the insufficient, or lack of, response of some children, leading to corrective surgeries of lower limbs(101);
- 212 – and the incomplete correction of muscle function deficits(75,76).

213 In addition to these major issues, we are lacking large scale studies to evaluate the impact of this conventional therapy on the quality of life and  
214 on the development of several disease complications such as craniosynostosis and hearing problems, enthesopathy, chronic pain and fatigue.

215

#### 216 **Dose Adjustment for conventional therapy (table 2)**

217 The daily dose of phosphate supplements and vitamin D analogues is adjusted to serum ALP and PTH and urinary calcium/creatinine  
218 concentrations, clinical measures (leg bowing, growth velocity) and the patient's weight. The goal is to maintain normal ALP, PTH and urinary  
219 calcium/creatinine levels but not to normalise serum phosphate levels. During the first months of treatment, consistently elevated ALP levels  
220 without hypercalciuria should lead to an increase in active vitamin D analogue and/or phosphate dose. *Vice versa*, normalized ALP in the  
221 presence of hypercalciuria may require a reduction in the dose of active vitamin D analogues. If PTH level increases, one must consider  
222 lowering phosphate supplementation and/or increasing the dose of active vitamin D analogues. In all cases, strict adherence to medication, in  
223 particular the multiple daily dosing of phosphate is essential.

224

### 225 **5.3 Novel therapy with anti-FGF23 antibody**

226 As for today, the alternative therapy is burosumab, the humanized monoclonal anti-FGF23 antibody which was recently approved in the  
227 European Union for the treatment of XLH children over 1 year of age and adolescents who are still growing, and in the US for the treatment of  
228 all patients affected by XLH over 1 year of age(102,103). The main objective of this treatment is to counteract excess FGF23, thereby restoring  
229 phosphate reabsorption and endogenous 1,25(OH)<sub>2</sub> vitamin D synthesis.

230 In children with severe XLH aged 5 to 12 years, the treatment with burosumab, given subcutaneously every 2 weeks was found to result  
231 in(104):

- 232 – a steady increase in serum phosphate concentration to a range between 1.1 and 1.6 mmol/l due to an increase in TmP/GFR;
- 233 – an increase in the calcitriol levels;
- 234 – an improvement in the radiographic rickets severity scores after 40 and 64 weeks of treatment;
- 235 – an improvement of physical function as shown by the increase in the distance walked during the 6MWT.

236 In contrast to conventional therapy, the burosumab dose is adjusted to the serum phosphate concentration as described in table 2. The  
237 recommended starting dose in Europe is 0.4 mg/kg body weight (0.8 mg/kg in US), followed by a titration period to reach a serum phosphate  
238 level in the low normal range for age, through dose increments every 4 weeks (maximum dose 2.0 mg/kg body weight or 90 mg every 15 days).

239

240 The limitations known to this treatment are(104–106):

- 241 – injections site reactions, headache and muscular pain;
- 242 – gain in growth velocity appears limited;
- 243 – the therapy is recent and therefore data on any long-term outcomes, e.g. hyperparathyroidism, nephrocalcinosis, surgery, body  
244 disproportion and adult complications such as enthesopathy are not yet available.

245

246 Given the available evidence for both therapies, we propose that children born into families affected with XLH, as well as children with a *de*  
247 *novo* diagnosis of XLH, be started on conventional therapy except if the diagnosis was delayed for several years, thus rickets considered as  
248 severe. In our view, treatment with burosumab should be offered (unless of course injections are refused), preferably with rigorous  
249 documentation and follow-up, to XLH children aged 1 year or older and in adolescents with growing skeletons if:

- 250 - they have radiographic evidence of rickets;
- 251 - they are refractory to conventional therapy;
- 252 - they experience complications related to conventional therapy.

253

## 254 **6. DISEASE FOLLOW-UP (table 2)**

255 Adequate follow-up of XLH patients includes clinical, biochemical and radiological monitoring of treatment (efficacy and complications) and  
256 screening for XLH-related dental, neurosurgical, rheumatological, cardiovascular, renal and/or ENT complications(20,30).

257 The parameters, as well as their frequency of assessment vary depending on age, disease severity and existing XLH-related complications.

258

### 259 **6.1 Treatment monitoring**

260 Clinical follow-up includes measuring intercondylar distance, intermalleolar distance, and if possible tibial torsion(107), height and growth  
261 velocity. An annual 6MWT can also be helpful in older children (from 5-6 years of age)(104,108). The number of dental abscesses and  
262 episodes of acute oral infections are recorded. The rachitic/osteomalacic, insufficiently treated bone, is associated with elevated ALP and low  
263 urinary calcium. In contrast, when rickets is healing, ALP tends to normalize, and urinary calcium to increase. The FGF23 level is not used as a  
264 tool for treatment monitoring in XLH children(33,109,110).

265 The efficacy and safety of conventional therapy, i.e. phosphate supplements and vitamin D analogues, is monitored by measuring ALP, the  
266 biomarker of rickets activity and osteomalacia(20,66,82,85). PTH is measured regularly as hyperparathyroidism is promoted by oral phosphate  
267 supplementation, especially during adolescence(8,86,91,111). Serum and specifically urine calcium measurements are necessary to evaluate  
268 the safety of vitamin D analogues. In children younger than 5 years of age, the 24 hours urine collection is quite difficult, and spot urine samples

269 are preferred. In children older than 5 years of age, 24 hours urine collections are advised if the urinary calcium is above the upper limit of  
270 normal ( $\text{Uca/cr} > 0.7 \text{ mmol/mmol}$ )(112).

271 The follow-up of children with rickets may include radiographs. Once the diagnosis is made, radiological techniques using small amounts of X-  
272 rays, such as EOS, may be used whenever possible. Radiographs of lower limbs or knees (done not more than every 2 years) may be useful  
273 during follow-up. Radiographs may be indicated if patients are refractory to therapy, if orthopedic surgery is indicated, in cases of unexplained  
274 bone pain and before transition to adult care.

275 After initial treatment initiation and during physiological periods of rapid growth (infancy and puberty) it is useful to evaluate the patient every  
276 three months clinically and biochemically. This is also the case for patients of all ages with unsatisfactory results, e.g. ALP remaining high,  
277 worsening of leg bowing, or pain. Otherwise 6-monthly evaluation is sufficient.

278

279 The questions that should be asked if treatment objectives under conventional therapy are not achieved are:

280 Is treatment correctly prescribed?

- 281 • Are the doses appropriate? Adjusted to weight and growth velocity? Adjusted to biochemical markers?
- 282 • Are phosphate supplements prescribed in multiple daily doses?
- 283 • Is treatment correctly given? Are phosphate supplements given separately from calcium intakes such as milk and yogurt?
- 284 • Is compliance correct? As in many chronic diseases that require multiple daily doses of medication, poor compliance often explains poor  
285 metabolic control and poor clinical outcome.

286

## 287 **6.2 Particular aspects concerning patients treated with burosumab**

288 In patients treated with burosumab, serum phosphate is a strong biomarker of efficacy and is monitored for treatment titration and follow-up. In  
289 clinical trials, the phosphate target ranges from 1.1 to 1.6 mmol/l. Measurements are performed every 2 later every 4 weeks (104) for dose  
290 adjustment. We do not yet know the optimal serum phosphate target for children. During treatment, TmP/GFR and ALP require monitoring  
291 since they act as short-term and long-term biochemical markers of burosumab efficacy, respectively(104). The  $1,25(\text{OH})_2$  vitamin D

292 concentration increases rapidly upon burosumab therapy during 64 weeks of observation ; its value as a biomarker to adjust the therapy has  
293 not been evaluated(105,113,114).

294

## 295 **7. SCREENING FOR XLH COMPLICATIONS**

296 **Craniosynostosis and premature fusion of cranial sutures** are complications of XLH. Craniosynostosis should be screened for by  
297 assessing head circumference, skull shape and also neurological signs (fundoscopy, headaches). To date, there are no clear guidelines  
298 regarding MRI evaluations of children with XLH. However, recent data demonstrated the high frequency of Chiari 1 malformation and  
299 syringomyelia in XLH children raising the question whether systematic evaluation of the brain through MRI during childhood is indicated  
300 (55,60,115). In case of neurological symptoms, a CT scan and/or brain MRI should be done.

301 **Hearing** should be evaluated by audiometry during childhood; however data to identify the best time period or at risk patients is scarce(62).

302 **Dental** examination should be performed at least once a year in children(9). For details refer to the dedicated article on dental issues.

303 **Growth** should be monitored at least twice a year; bone age evaluation may be included in short children or in case of decreased growth  
304 velocity, a sign of active rickets which may require an increase in therapy(10,11,20,41,68,69). Growth hormone (GH) is not a standard  
305 treatment or indication for children with XLH. Studies have shown that GH increases short-term linear growth in short XLH children before  
306 puberty(116–123). Data on only 5 patients treated until final height showed no significant gain(124).

307 **Nephrocalcinosis and nephrolithiasis** are screened for using kidney ultrasounds and should be done at the start of therapy and  
308 approximately every 1-2 years depending on the urinary excretion of calcium(125).

309 **Cardiovascular screening.** To date, cardiac complications of XLH, on conventional therapy, are not commonly reported. This is surprising  
310 given that FGF23 has long been known to be associated with cardiovascular risk and the development of pathological hypertrophy that can lead  
311 to congestive heart failure(126). Only very recently was left ventricular hypertrophy and hypertension described in a subset of XLH patients in a  
312 prospective clinical study(127). Given the sparse evidence, it is difficult to come up with firm recommendations. We have decided to  
313 recommend cardiac echography every 5 years until further evidence emerges. Regular cardiac ultrasound measurements were part of the  
314 safety features of the burosumab clinical trials with no evidence of complications. Given the limited long-term safety data, we feel that regular  
315 echocardiography is required until more evidence emerges.

316

## 317 **8. SOCIAL AND PATIENT EDUCATION FOLLOW-UP**

318 Education of patients and families is crucial at the time of diagnosis. Regular updates are necessary to assess and encourage adherence to  
319 treatments, provide service contacts and information about patients' association groups, inform patients of scientific discoveries, including new  
320 therapies, support school and professional achievement and provide adequate social support (e.g. XLHnetwork.com; [\(1\)](#); [http://](http://phosphatdiabetes.de)  
321 [phosphatdiabetes.de](http://phosphatdiabetes.de)).

322

## 323 **9. PERSPECTIVES**

324 XLH is a multisystemic disorder that may manifest in children only once they start standing and walking. Untreated, or insufficiently treated, the  
325 disease leads to severe handicaps including bone pain, bone deformities, dental complications with abscesses and missing teeth, and short  
326 stature. The current conventional therapy, based on phosphate supplements and vitamin D analogues allows improvement in bone deformities,  
327 growth velocity and bone and dentin mineralization. However, this treatment does not restore normal phosphate levels and many patients do  
328 not respond fully/adequately to this therapy. Burosumab counteracts FGF23 excess thus restores renal phosphate reabsorption in treated  
329 children and adolescents. These convincing results have led to the approval of burosumab by EMA and FDA for the use in Europe and the  
330 USA. However, long-term data are needed, especially on growth, renal calcium excretion, PTH secretion and bone disease overall. When  
331 children evolve through adolescence and then adulthood, complications of their disease such as hearing impairment, hyperparathyroidism,  
332 cardiovascular and renal complications, rheumatological issues and enthesopathy may occur. These complications, which may be modified by  
333 the disease's therapy, render difficult the decision to stop or pursue the daily conventional treatment through adulthood once growth is  
334 complete. Since osteomalacia will return after any of the two therapies is stopped, adult bone specialists will need to gather further long-term  
335 treatment data.

336

## 337 **Contributors**

338 AR and AL wrote the initial draft of the article.

339 All authors contributed equally in the construction and the revision of the article.



340 All authors read and approved the final manuscript.

341

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348

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356 **Figure 1:** Radiographic features of rickets in XLH children

357 **A.** Radiographs of lower limbs in a baby girl with an affected XLH father carrying a *PHEX* mutation. The baby is also affected; there are almost  
358 no signs of rickets on radiographs at birth. Treatment was started on day 7 with alfacalcidol 1ug/day (27 ng/kg/d) and phosphate supplements  
359 (Phosphoneuros®) 80 mg, 4 times per day (60 mg/kg/d) given twenty minutes after breast feeding. On radiographs at age 2.5 years, there were  
360 no signs of rickets (mild features at year 1). **B.** Different features of rickets, highlighting the variability in XLH disease severity, at the time of  
361 diagnosis in three children diagnosed late with *de novo PHEX* mutations.

362

363 **Figure 2:** Diagnosis of XLH in children

364 **A.** Age at diagnosis in children affected with XLH; we selected only the *de novo* cases (n=36 out of 94). The cohort of patients is followed at the  
365 Bicêtre reference center, Paris, France (unpublished). The mean age (+/- SD) at diagnosis (dotted line) was  $3.9 \pm 3.1$  yrs, the median was 2.7  
366 yrs [min: 0.9 - max:13.7] yrs. Each bar represents a case. **B.** Physiological distance between knees and ankles in children, adapted from. The  
367 upper part of the graph represents the 2SD intercondylar distance (positive) and the lower part the 2 SD intermalleolar distance (negative) and  
368 the mean values are represented in the middle of the graph. **C.** Serum ALP concentrations in 21 children with XLH at the time of diagnosis  
369 compared with 7 children affected by a molecular defect in the calcitriol (VDR) receptor. Median and 5<sup>th</sup> - 95<sup>th</sup> percentile of ALP are given.

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373 **Table 1:** Diagnostic work up for XLH and differential diagnosis of hypophosphatemia

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	<b>Newborn Familial</b>	<b>Child Familial</b>	<b>Infant-Child De novo</b>
			Take family history of leg bowing in infancy, dental problems, chronic 'rheumatological' pain and short stature
<b>Radiographs</b>		Left hand and wrist Standing lower limbs	Left hand and wrist (=bone age) Standing lower limbs
<b>Blood biochemistry</b>	Phosphate, calcium ALP Creatinine PTH	Phosphate, calcium ALP Creatinine PTH	Phosphate, calcium ALP Creatinine PTH 25OHD; 1,25(OH) <sub>2</sub> D Electrolytes, blood gas
<b>Urine biochemistry</b>	Phosphate Creatinine Calcium	Phosphate Creatinine Calcium	Phosphate Creatinine Calcium Electrolytes Protein, aminoacids
<b>Confirmation</b>	<i>PHEX</i> genetics	<i>PHEX</i> genetics	Intact FGF23 <i>PHEX</i> genetics

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376 25OHD: 25-hydroxy vitamin D; 1,25(OH)<sub>2</sub>D: 1,25-di-hydroxy vitamin D (calcitriol)

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384 **Table 2:** Treatment doses, objectives and monitoring in children affected with XLH

Table 11. Treatment doses, objectives and monitoring in children affected with XLH				
		Vitamin D analogs and phosphate supplements		Burosumab
		Newborns or before the development of clinical or radiological signs of rickets	Clinical or radiological signs of rickets	Children > 1 year
Treatment doses	Starting dose	Alfacalcidol: 25-40 ng/kg/day (0.8-1 ug/day) Phosphate: 40-60 mg/kg/day (4 to 5 intakes/day)	Alfacalcidol: 40-80 ng/kg/day (1-1.5 ug/day) Phosphate: 40-60 mg/kg/day (4 to 5 intakes/day)	0.4 mg/kg/15 days in Europe 0.8 mg/kg/15 days in USA
	Maintenance dose	Alfacalcidol: 25-40 ng/kg/day (1-2 ug/day) Phosphate: 30-60 mg/kg/day (3 to 5 intakes/ day)		~ 1 mg/kg of body weight every 15 days
Efficacy markers	Outcomes	Time to the objective		
	Normal serum phosphate	Non applicable		1-4 months
	Normal urinary excretion of phosphate (TRP, TmP/GFR)			
	Increase in 1,25 (OH)2D without hypercalcemia			
	ALP normalization	6-12 months		
	Improvement of lower limb deformities	3-4 years		Data not available
	6MWT	No data		Improvement at 12 months
	Increase in growth velocity	1 year		No data
	Improvement of radiological signs of rickets on radiographs of lower limbs (RGI-C)	No data		10 months

	Improvement of POSNA, PODCI	No data	10 months
<b>Safety markers</b>		Frequency of follow-up	
	Serum calcium	3-6 months	
	Urinary calcium		
	Serum PTH		
	Renal ultrasound	1-2 years	
	Cardiac ultrasound	Every 5 years	Every 2 years until more evidence available

385  
386 TRP: fractional tubular reabsorption of phosphate  
387 TmP/GFR: ratio of the renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate  
388 ALP : alkaline phosphatase  
389 6MWT : 6-minute walk test  
390 RGI-C: radiographic global impression of change  
391 POSNA: pediatric musculoskeletal functional health questionnaire  
392 PODCI: pediatric outcomes data collection instrument

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**Table 3:** Non-exhaustive list of the causes of rickets associated with renal phosphate wasting. \*

Disorder (abbreviation)	OMIM	Gene/location	Urinary Calcium	FGF23
<b>Rickets/osteomalacia with renal tubular phosphate wasting due to elevated FGF23 levels/signaling</b>				
X-linked hypophosphatemia (XLH)	#307800	PHEX/Xp22.1	Low Undetectable	Normal or moderately elevated
Autosomal dominant hypophosphatemic rickets (ADHR)	#193100)	FGF23/12p13.3	Low Undetectable	Elevated
Autosomal recessive hypophosphatemic rickets 1 (ARHR1)	#241520	DMP1/4q22.1	Low Undetectable	Normal or moderately elevated
Autosomal recessive hypophosphatemic rickets 2 (ARHR2)	#613312	ENPP1/6q23.2	Low Undetectable	Normal or moderately elevated
Hypophosphatemic rickets and hyperparathyroidism	#612089	KLOTHO/13q13.1	Low	Elevated
Osteoglophonic dysplasia (OD)	#166250	FGFR1/8p12	Low	Normal or moderately elevated
Fibrous dysplasia (FD) Tumor induced osteomalacia (TIO) Cutaneous skeletal hypophosphatemia syndrome (CSHS) also called Schimmelpenning-Feuerstein-Mims syndrome (SFM)	#174800  #163200	GNAS/20q13.3  RAS/1p13.2	Low Undetectable	Normal or moderately elevated
<b>Rickets/osteomalacia due to primary renal tubular phosphate wasting</b>				
Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)	#241530	SLC34A3/9q34.3	Normal or high	Low or undetectable
X-linked recessive hypophosphatemic rickets (XLR, Dent's disease, Lowe syndrome)	#300554 #309000	CLCN5/Xp11.23 OCRL1/Xq25-26	Normal or high	Varies
Renal Fanconi syndrome due to cystinosis	#219800	CTNS/17p13.2	High	Low
Hypophosphatemia and nephrocalcinosis (NPHLOP1) Fanconi reno-tubular syndrome 2 (FRTS2)	#612286 #613388	SLC34A1/5q35.3	Elevated	Low or undetectable
Iatrogenic proximal tubulopathy = drug induced Fanconi Syndrome (for instance cisplatin, ifosfamide, tenofovir, sodium valproate)			Varies	Variable

396 \* excluding causes of rickets with secondary phosphate wasting due to high PTH levels such as nutritional rickets, and rickets due to vitamin D  
397 deficiency or resistance.  
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